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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,522	08/15/2005	Andrew Powell	4033.3000 US	2122

38473 7590 09/18/2008

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
09/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,522	POWELL ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *16-22,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants again traverse the restriction between Groups I and VIII, albeit Groups I-VII have been rejoined. Applicants acknowledged that while it is true that Group VIII requires an additional step of screening compounds, the fact that an additional step is articulated does not justify restriction. Indeed, the claims include the same technical feature defined by Claim 1 and, thereby, possess unity of invention. In fact the inventions of the two claims could be viewed as being a combination (Group VIII) and subcombination (Group I). Restriction between these classes of invention requires two way distinctness. Because the combination (Claim 16) as claimed cannot be practiced without utilizing the subcombination as claimed (Claim 1), the Examiner simply cannot establish two way distinctness. As such, restriction is improper. See PCT Administrative Instructions Annex B(c)(i) and MPEP 806.05(c).

In reply, under PCT rule 13.1, the special technical features of Groups I and VIII define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art, as evidenced from the various prior art below.

Claims 16-22 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Status of Claims

Claims 1-25 are pending.

Claims 16-22 and 24-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention,

Claims 1-15 and 23 are under examination.

Withdrawn Objection/Rejection

In view of the amendments to the specification, the objection has been withdrawn. Also, the rejection under 35 USC 101, 35 USC 112, 2nd paragraph and 35 USC 102 over Wu or Ben-Artzi or de Born or Maccarana et al or Petitou et al are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim to an "in vitro" method of making a library is not supported in the as-filed specification and goes against the teachings in the instant disclosure. The original disclosure discloses an in vitro method of assay. There is no disclosure of how the library is produced by in vitro method. Thus, the scope of the in vitro method of the claimed method is not described in the specification. Also, the claimed proviso that "wherein at least one modification in said combination is a partial modification" has no support in the original disclosure. MPEP 714.02 clearly states that applicants specifically point out where in the original specification support for the newly added claim limitations appear.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-15 and 23, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Ben-Artzi (6190875)or Wu et al (The FASEB Journal, 4/2002) or de Born(The Jrnl. of Biological Chemistry, 1995) or Maccarana et al (The Jrnl. of Biological Chemistry, 1993) or Petitou et al (Eur. J. Biochem.) Or Baumann or Ungarelli (hereinafter the primary references) in view of Kariya or applicants' disclosure of known prior art for reasons as stated in the last Office action and repeated below.

A). Wu et al discloses throughout the published article at e.g., page 539, abstract a method of making a heparin sulfate derivative comprising of 3-O, 6-O sulfates and the minimal length of oligosaccharide antithrombin iii(at-iii) binding. The binding sites for AT-III is regenerated on completely desulfated N-resulfated heparin and revealed the critical modification enzymes. The method could be used to identify critical functional groups on HS, and to generate HS library.

Wu et al further disclose at e.g., col. 2, page 539:

> HS is initially synthesized in the Golgi apparatus as a nonsulfated copolymer attached to HS proteoglycan core proteins by sequential addition of D-glucuronic acid alternating with N-acetyl D-glucosamine. This is followed by various modification steps **including N-deacylation and N-sulfation of glucosamine, epimerization of GlcA to L-iduronic acid, S-O sulfation of uronic acid and 6-O sulfation and 3-O sulfation of glucosamine. All steps are catalyzed by different enzymes and the process is selective as to the position and number of modifications in a chain leading to extensive sequence diversity.**
>
> Wu also discloses at e.g., page 540, col. 1 and col. 2 a method combined with in vitro modification and gel mobility shift assay (GMSA) to reveal the structural features of heparin oligosaccharide, which recognized and activates AT-III.

Wu discloses at the RESULTS section the method of making a library with the interaction between a pentasaccharide and AT-III wherein the starting pentasaccharide lacks a 3-O sulfation and a 6-O sulfation. The modified pentasaccharide showed binding for AT-III of 6-O. At page 542, col. 2, first complete paragraph up to page 543, Wu discloses that since the most critical modifications for AT-III binding are 3-O and 6-O sulfations, reconstitution at AT-III binding sites on completely desulfated and N-resulfated heparin sulfate (DSNS) is made by addition of 3-O and 6-O sulfates to the chain (which reads on claim 15 steps of forming a library based on the function of a modified HS). DSNS was first modified with different combinations of sulfatransferases. The modified chain strongly bound to AT-III

and further addition of 2-O did not change the binding significantly. This proved it is possible to generate HS libraries and reconstitute protein binding sites on DSNS chain by in vitro modification.

B). Ben Artzi discloses throughout the disclosure at e.g., col. 4, lines 43-57:

> A "combinatorial" synthesis of a diverse set of molecules in which several components predicted to be associated with the desired biological activity are systematically varied (reads on claim 1 and claim 15).
>
> Ben-artzi further discloses in the Examples at e.g., col. 17, line 43 up to col. 18, line 25:
>
> … Chemically modified non-anticoagulant species of heparin were prepared from native heparin and heparin fragment….. Briefly, the pyridinium salt of heparin and heparin fragment underwent complete N-desulfation……Total desulfation of N and O sulfate groups was obtained by exhaustive desulfation…… The N-desulfated heparin fragment was N-acetylated……. or N-resulfated with sulfur trioxide trimethylamine complex, as described (20). An O-desulfated, N-acetylated heparin fragment was obtained by O-desulfating an N-acetylated heparin fragment as described (20, 22).(Reads on claim 1). Intact heparin was chemically modified by the same procedures. These modified heparins exhibited <5% of the anticoagulant activity of heparin (23). (Reads on claim 15.) See further the detailed description in the Examples starting at col. 15, Example 1.

C). De Born discloses throughout the published article, a method of making a library by modifying heparin sulfate by the process of desulfation, resulfation and 0-desulfation, **partial or complete**. See e.g., page 31303, col. 1, the abstract.

D). Maccarana et al discloses throughout the published article, a method of making a library by modifying heparin sulfate by the process of desulfation, resulfation and 0-desulfation, **partial or complete**. See e.g., page 23898, Experimental Procedures and Fig. 7, page 23903.

E). Petitou discloses throughout the published article, a method of making a library by modifying heparin sulfate by the process of desulfation, resulfation and 0-desulfation, **partial or complete**, at e.g., page 637, Material and methods section.

F). Baumann et al at discloses specific process steps of making a library of HS by combining the different specific steps at e.g., page 383, col. 1, including the Table, up to page 387, col. 2.

G). Ungarelli discloses throughout the patent at e.g., col. 4, line 60 up col. 8 a process of producing a library with the structural formula as shown. The formula of Ungarelli which contains different substituents for each of the variables e.g., R and Z reads on the claimed library. These variables define the claimed modifications of e.g., sulfation, de-sulfation and so on. Note that N3 without the sulfur group indicates the N has been desulfated. See further the Examples and claims.

Each of these references does not teach complete de N-sulfation in glucosamine. However, Kariya throughout the article discloses at e.g., page 25949 col. 2:

> Solvolysis of heparin affords complete removal of N-sulfate groups from GlcN residues, removal of a substantial part of 2-O-sulfate groups from iduronic acid(Id-oUA) residues, and incomplete removal of 6-O-sulfate groups from GlcN residues, which occur even under the most optimized conditions (35). Accordingly, the heparin derivative prepared by the subsequent N-resulfation contains significantly reduced amounts of 2-O-sulfate groups of IdoUA residues…

It would have been obvious to one having ordinary skill in the art at the time the invention was made to make a library of the known derivatives of heparin sulfate as taught by each of Ben-artzi, Wu, de Born or Maccarana or Petitou with complete N-sulfate removal in the GlcN residues as taught by Kariya. Kariya teaches said N de-sulfation by solvolysis occur under the most optimized conditions. N-desulfation of glucosamine in the method of any one of the above cited primary references would be expected to produce a predictable result. N-modification has been known or used either singly or in combination with the other modifications known in the art. N-desulfation of glucosamine is known in the art as one of the modifications

that heparan sulfate undergoes even in its biosynthesis. One having ordinary skill in the art would have been motivated to employ N-desulfation step to obtain a library with an optimized result. One would expect that N-desulfation in combination with the other modifications as taught in anyone of the primary references would yield a more diverse library. Ben-artzi teaches that the combinatorial library provides the advantage for screening for desired biologically active compounds when all the components comprising the library are known in advance. Applicants discloses at pages 1-5 particularly, page 5 of the instant disclosure:

> Several examples of apparent chemical modification to heparin, HS or related GAGs can be found in the patent literature, for example, US 5,430,133, US 5,405,949, US 5,543,403, US 5,958,899, US 4,717,719 and EP0380719. In. 15 particular, selective de-O-sulfation at iduronate-2-sulfate groups employing highly basic conditions. This modification is intended to result in selective removal of 2-O-sulfate groups from iduronate; in fact, it also results in the introduction of unnatural modifications (in the small amounts of N,3 disulfated and N,3,6 trisulfated glucosamine residues present in heparin, see Yates et al, 20 Carbohydr.Res., (1997) 298 335-340) while its incomplete application introduces epoxide groups in the iduronate residues (see M.Jaseja et al, Can.J.Chem., (1989) 67 1449-1456). The present invention does not rely on the. introduction of any such abberant substitutions.

Response to Arguments

Applicants assert that the claims have been amended to require three steps selected from A to O wherein at least one chemical modification is partial. Each of the references cited by the Examiner disclose chemical modification of a heparin sulfate starting material but none of the references teaches the specific combination of steps required by the present claims. Specifically, none of the primary references discloses the three steps selected from A to O, wherein at least one chemical modification is partial. The teaching of Kariya et al. does not remedy this deficiency. Kariya et al. discloses only two chemical modification steps. There is no teaching in the primary references or in Kariya et al. that would render the presently claimed method obvious.

In reply, as acknowledged by applicants above, Kariya discloses already two chemical modifications steps while the other references e.g., Wu et al discloses at least one chemical modification. Even assuming that the primary references does not teach partial modification (which each does however), such partial modification would be within the ordinary skill in the art to do. Please note the positive disclosure of said partial modification by anyone of de Born or Maccarana or Petitou. One

having ordinary skill in he art would obviously know when to stop a reaction when one so desires only partial reactions, as evidenced by e.g., de Born above. Accordingly, the combined teachings of the art would lead one having ordinary skill in the art to the at least three combined modifications to make a library.

In considering disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also **inferences** which one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 159 USPQ 342; In re DeLise 160 USPQ 806. The test for combining references is not what the individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 CCPA 1971.

The court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art. In re Kuderna, 165 USPQ 575 CCPA 1970. Rather, as held by the majority in Merck & Co. Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 10 USPQ 2d 1843 (Fed. Cir. 1989), at 10 USPQ 2d 1846:

> That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition

> is used for the identical purpose taught by the prior art. See In re Corkill, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among "thousands of compounds"); In re Susi, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellants generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." . . [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known inthe field, the combination must do more than yield a predictable result." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007) 2141 to 2145.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is

reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 16-22 and 24-25 drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639